acids;

(b) subjecting the one or more target nucleic acids obtained from step (a) to a set of separate base-specific, sequence-specific or site-specific complementary cleavage reactions, wherein each cleavage reaction generates a non-ordered set of fragments;

(c) analyzing the sets of non-ordered fragments obtained from step (b) by mass spectrometry; and,

(d) performing a systematic computational analysis on the mass spectra obtained from step (c) to analyse the sequence of said target nucleic acid,

wherein said complementary cleavage reactions refer to target nucleic acid digestions characterized by varying specificity and/or to digestion of alternative forms of the target sequence.

58. [NEW] The method according to claim 57 wherein the one or more biological samples are derived from organism selected from the group consisting of eukaryotes, prokaryotes, and viruses.

59. [NEW] The method according to claim 57 wherein the one or more target nucleic acids are selected from the group consisting of single stranded DNA, double stranded DNA, cDNA, single stranded RNA, double stranded RNA, DNA/RNA hybrid, and DNA/RNA mosaic nucleic acid.

60. [NEW] The method according to claim 57 wherein one or more target nucleic acids are derived by one or more consecutive amplification procedures selected from the group consisting of in vivo cloning, polymerase chain reaction (PCR), reverse transcription followed by the polymerase chain reaction (RT-PCR), strand displacement amplification (SDA), and transcription based processes.

61. [NEW] The method according to claim 4 wherein the one or more amplified target nucleic acids are transcripts generated from a single stranded or a double stranded target nucleic acid by a process comprising the steps of:

(a) linking operatively a transcription control sequences to the one or more target nucleic acids; and

(b) transcribing one or both strands of the one or more target nucleic acid of step a) using one or more RNA polymerases that recognize the transcription control sequence on the one or more target nucleic acids.

62. [NEW] The method according to claim 61 wherein said transcriptional control sequences are operatively linked to one or more target nucleic acids by PCR amplification using primers that incorporate the transcriptional control sequences as 5'-extensions.

63. [NEW] The method according to claim 61 wherein the transcription control sequence is selected from the group consisting of eukaryotic transcription control sequences, prokaryotic transcription control sequences, and viral transcription control sequences.

64. [NEW] The method according to claim 63 wherein the prokaryotic transcription control sequence is selected from the group consisting of T3, T7, and SP6 promoters.

65. [NEW] The method according to claim 64 wherein the RNA polymerases which utilize the T3, T7, or SP6 promoters are either wild type or mutant RNA polymerases, the mutant polymerases being capable of incorporating into the transcript non-canonical substrates with a 2'-deoxy, 2'-O-methyl, 2'-fluoro or 2'-amino substituent.

66. [NEW] The method according to claim 65 wherein the mutant RNA polymerase is either T7 or SP6 mutant polymerase.

67. [NEW] The method according to claim 57 wherein the derived target nucleic acid incorporates one or more nucleosides that are modified on the base, the sugar, and/or the phosphate moiety, wherein the modifications alter the specificity of cleavage by the one or more cleavage reagents and/or the mass and/or the length of the cleavage products.

68. [NEW] The method according to claim 67 wherein the modification is

introduced through the enzymatic incorporation of modified deoxynucleoside triphosphates, modified ribonucleoside triphosphates, and/or modified dideoxynucleoside triphosphates; or wherein the modification is introduced chemically, or wherein the modification is introduced through a combination of both methods.

69. [NEW] The method according to claim 67 wherein the modification consists of a 2'-deoxy, 2′-O-methyl, 2'-fluoro or 2'-amino substituent on the nucleotide triphosphates.

70. [NEW] The method according to claim 67 wherein the modification consists of phosphorothioate internucleoside linkages or phosphorothioate internucleoside linkages further reacted with an alkylating reagent.

71. [NEW] The method according to claim 67 wherein the modification consists of a methyl group on C5 of the uridine-5′-monophosphate subunits.

72. [NEW] The method according to claim 67 wherein the modification consists of nucleotides that incorporate alternative isotopes.

73. [NEW] The method according to claim 57 wherein the one or more target nucleic acids of step (a) are purified prior to cleavage.

74. [NEW] The method according to claim 73 wherein said purification is achieved through immobilization or by chromatography.

75. [NEW] The method according to claim 57 wherein the complementary cleavage reactions are selected from the group consisting of enzymatic cleavage, chemical cleavage, and physical cleavage.

76. [NEW] The method according to claim 75 wherein the complementary cleavage reactions are characterized by a relaxed mono-nucleotide, mono-nucleotide, relaxed di-nucleotide, or di-nucleotide specificity.

77. [NEW] The method according to claim 75 wherein the one or more target nucleic acids are subjected to chemical digestion reaction consisting of treatment with alkali or with reagents used in the Maxam & Gilbert sequencing method.

78. [NEW] The method according to claim 75 wherein the one or more target nucleic acids are subjected to enzymatic cleavage reaction using one or more enzymes selected from the group consisting of endonucleases and exonucleases.

79. [NEW] The method according to claim 78 wherein the one or more target nucleic acids are subjected to enzymatic cleavage reaction using one or more endonucleases, selected from the group consisting of restriction enzymes, RNA endonucleases, DNA endonucleases and non-specific phosphodiesterases.

80. [NEW] The method according to claim 79 wherein the one or more endonucleases are one or more selective or non-selective RNA endonucleases, selected from the group consisting of the G-specific T1 ribonuclease, the A-specific U2 ribonuclease, the A/U specific phyM ribonuclease, the U/C specific ribonuclease A, the C-specific chicken liver ribonuclease (RNaseCL3) and cusativin, non-specific RNase-I, and pyrimidine-adenosine preferring RNases isolated from E. coli, Enterobacter sp., or Saccharomyces cerevisiae.

81. [NEW] The method according to claim 57 wherein the one or more target nucleic acids are phosphorothioate-modified single stranded DNA or RNA, and wherein the cleavage reactions are performed with the nuclease P1.

82. [NEW] The method according to claim 57 wherein the one or more target nucleic acids are mosaic RNA/DNA nucleic acids or modified mosaic RNA/DNA nucleic acids, prepared with mutant polymerases, and wherein the cleavage reagents are RNA endonucleases, DNA endonucleases or alkali.

83. [NEW] The method according to claim 57 wherein the one or more target nucleic

acids are transcripts, modified transcripts, mosaic RNA/DNA transcripts or modified mosaic RNA/DNA transcripts, prepared with wild type or mutant RNA polymerases, and wherein the cleavage reagents are one or more selective or non-selective RNA endonucleases or alkali.

84. [NEW] The method according to claim 57 wherein the one or more target nucleic acids are mosaic RNA/DNA transcripts that incorporate either dCMP, dUMP or dTMP, prepared with mutant T7 or SP6 polymerase, and wherein the cleavage reagent is a pyrimidine-specific RNase, such as RNase-A.

85. [NEW] The method according to claim 57 wherein the set of non-ordered fragments of step (b) is additionally purified using an ion exchange beads.

86. [NEW] The method according to claim 57 wherein the set of non-ordered fragments of step (b) is spotted onto a solid support.

87. [NEW] The method according to claim 86 wherein said solid support is chosen from a group consisting of solid surfaces, plates and chips.

88. [NEW] The method according to claim 57 wherein the mass spectrometric analysis of the nucleic acid fragments is performed using a mass spectrometric method selected from the group consisting of Matrix-Assisted Laser Desorption/Ionization-Time-of-flight (MALDI-TOF), Electrospray-Ionization (ESI), and Fourier Transform-Ion Cyclotron Resonance (FT-ICR).

89. [NEW] The method according to claim 57 for sequence analysis of one or more target nucleic acids for which a reference nucleic acid sequence is known; comprising an additional step wherein the one or more mass spectra of the non-ordered fragments obtained in step c) are compared with the known or predicted mass spectra for a reference nucleic acid sequence, and deducing therefrom, by systematic computational analysis, all or part of the nucleotide sequence of the one or more target nucleic acids, and comparing the deduced nucleic acid sequence with the reference nucleic acid to determine whether the one or more

target nucleic acids have the same sequence or a different sequence from the reference nucleic acid.

90. [NEW] The method according to claim 89 wherein the nucleic acid sequence difference that is determined is a deletion, substitution, insertion or combinations thereof.

91. [NEW] The method according to claim 90 wherein the nucleic acid sequence difference is a Single Nucleic Polymorphism (SNP).

92. [NEW] Use of a method according to claim 89 for scoring known as well as unknown nucleotide sequence variations of one or more target nucleic acids present in one or more biological samples.

93. [NEW] Use according to claim 92 wherein the determination of said known or unknown nucleotide sequence variations allows the identification of the various allelic sequences of a certain region/gene, the scoring of disease-associated mutations, the detection of somatic variations, or studies in the field of molecular evolution.

94. [NEW] Use of a method according to claim 86 wherein the spectra obtained for one or more target nucleic acids are compared with the mass spectra predicted for a plurality of reference nucleic acids thereby identifying/detecting one or more target nucleic acids in one or more biological samples.

95. [NEW] Use according to claim 94 to determine the expression profile of one or more target nucleic acids in one or more biological samples.

96. [NEW] A method according to claim 57 for sequence analysis of one or more target nucleic acids of unknown sequence present in one or more biological samples, said method comprising the steps of:

(a) deriving from one or more biological samples one or more target nucleic acids in a single stranded form;

(b) subjecting the one or more target nucleic acids obtained from step (a) to a set of four separate base-specific complementary cleavage reactions, wherein each cleavage reaction generates a non-ordered set of fragments;

(c) analyzing the sets of non-ordered fragments obtained from step (b) by mass spectrometry;

(d) performing a systematic computational analysis on the mass spectra obtained from step (c) to assemble the sequence of said target nucleic acid; and,

(e) optionally, if the sequence is not uniquely defined after step (d), repeating steps (a) through (d), thereby generating modified forms of said target nucleic acid and/or different portions of said target nucleic acid, and performing supplementary mono- and/or di-nucleotide specific cleavage reactions rendering supplementary sets of non-ordered fragments until the combined data converge into a unique sequence solution,

wherein said complementary cleavage reactions refer to target nucleic acid digestions characterized by varying specificity and/or to digestion of alternative forms of the target sequence.

97. [NEW] Use of a method according to claim 96 for the sequence analysis of one or more target nucleic acids of unknown sequence present in one or more biological samples.

98. [NEW] Use of a method according claim 96 for the sequence determination of one or more target nucleic acids of unknown sequence present in one or more biological samples.

99. [NEW] Use of a method according to claim 89 for genome wide genotyping of one or more biological samples.

100. A kit for sequence analysis according to a method of claim 57 of one or more target nucleic acids for which a reference nucleic acid sequence is known in one or more biological samples using mass spectrometry, the kit comprising:

(a) one or more nucleotide triphosphates;

(b) one or more polymerases;

(c) one or more nucleic acid cleaving agents; and,

(d) one or more sets of reference nucleic acids for which the nucleic acid sequence is known;

(e) optionally, reagents to purify the target nucleic acid;

(f) optionally, ion exchange beads in order to purify the non-ordered set of fragments;

(g) optionally, a solid support whereon the non-ordered set of fragments may be spotted; and,

(h) optionally, computer software for comparing the mass spectra of the one or more target nucleic acid with the mass spectra of the reference nucleic acid and deducing therefrom the nucleic acid sequence of the target nucleic acid.

101. [NEW] Use of a kit according to claim 100 for analyzing the sequence of, for determining sequence differences in, for scoring known as well as unknown nucleotide sequence variations in, for detecting/identifying, or, for performing genome wide genotyping using one or more target nucleic acids, for which a reference nucleic acid sequence is known, present in one or more biological samples.

102. [NEW] A kit for sequence analysis according to a method of claim 57 of one or more unknown target nucleic acids in one or more biological sample using mass spectroscopy, the kit comprising:

(a) one or more nucleotide triphosphates;

(b) one or more polymerases; and,

(c) one or more nucleic acid cleaving agents;

(d) optionally, reagents to purify the target nucleic acid;

(e) optionally, ion exchange beads in order to purify the non-ordered set of fragments;

(f) optionally, a solid support whereon the non-ordered set of fragments may be spotted; and,

(g) optionally, computer software for analysing the sequence of said target nucleic